PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Robert Yongxin ZHAO, et al.

Docket No: A8671

Appln. No.: 10/692,856

Group Art Unit: 1626

Confirmation No.: 9247

Examiner: Rei Tsang Shiao

Filed: October 27, 2003

For: IMPROVED PRODRUGS OF CC-1065 ANALOGS

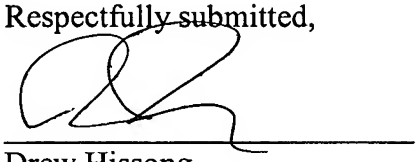
SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a copy of an executed Declaration Under 37 C.F.R. §1.132 signed by Walter A. Blättler, Ph.D..

Respectfully submitted,



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Date: January, 31, 2005

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DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Walter A. Blättler, hereby declare and state:

THAT I am a citizen of Switzerland;

THAT I received an M.S. degree in Chemistry in 1973 from the Swiss Federal Institute of Technology, Zurich (ETH Zürich);

THAT I received a D.sc.nat. in Chemistry in 1978 from the Swiss Federal Institute of Technology, Zurich (ETH Zürich);

THAT I was a Postdoctoral Fellow in the Chemistry Department at Harvard University, Cambridge, MA from 1978-1981;

THAT I was an Associate in Pathology at the Dana Farber Cancer Institute, Harvard Medical School, Boston, MA from 1981-1986;

THAT I was an Assistant Professor in Pathology at the Dana Farber Cancer Institute, Harvard Medical School, Boston, MA from 1986-1987;

THAT I was a Lecturer in Pathology at the Dana Farber Cancer Institute, Harvard Medical School, Boston, MA from 1987-1996;

THAT in 1987 I joined ImmunoGen, Inc. as Vice-President Research, and remained in that position until 1994;

THAT from 1994 to 1996 I was Senior Vice-President, R & D, at ImmunoGen, Inc. Cambridge, MA;

THAT in 1996 I was promoted to Executive Vice President, Science and Technology at ImmunoGen, Inc., Cambridge, MA, and remain in that position today;

A copy of my curricular vitae is attached.

I further declare and state as follows:

I. INTRODUCTION

I am familiar with the Office Action dated October 25, 2005, issued in the above-identified application and with the Examiner's position that the present claims should be limited to reciting analogs of CC-1065 for which specific formulas are identified in the application. Specifically, the Examiner asserts that there is no written description of other CC-1065 analogs. I understand this to mean that the Examiner is asserting that the inventors, of which I am one, did not have possession of other analogs of CC-1065 as of the effective filing date of the present application.

I further understand that the Examiner is asserting that the claims are not enabled for a prodrug of an analog of CC-1065, wherein the analog is not one specifically defined by a formula in the specification. I understand this to mean that the Examiner believes that one of

ordinary skill in the art would not have known how to make and use prodrugs of other analogs of CC-1065 as of the effective filing date of the present application.

For the following reasons, the Examiner's position is at odds with the state of the art as it existed at the time of the effective filing date of the present application.

II. THE APPLICATION CONTAINS A WRITTEN DESCRIPTION OF A BROAD GROUP OF CC-1065 ANALOGS AND PRODRUGS THEREOF

There are many published reports (as examples see the list of references given) describing the preparation of CC-1065 analogues. Therefore this class of compounds is well defined.

The natural cytotoxic antibiotic CC-1065 is composed of two structural elements with separate functions. The CPI element (cyclopropa[c]pyrrolo[3.2-e]indol-4(5H)-one element) covalently alkylates DNA and the element containing two benzo[1,2-b:4,3-b']dipyrrole moieties binds to DNA. When CC-1065 was tested in animals it caused delayed lethality, which prevented its use in humans. A quote from ref. 8, first page, second paragraph: "To pursue compounds retaining the potent antitumor activity but devoid of the toxic side effects of the parent compound, many CC-1065 analogues have been synthesized and tested." To retain the potent antitumor activity, the two functions, i.e. DNA alkylation found in the first element, and the DNA binding function found in the second element, had to be retained. Therefore CC-1065 analogues will mimic the CPI element and the benzodipyrrole element.

The first set of analogs published (ref. 1) altered the binding element but retained the CPI element. A second series changed the CPI element (cyclopropa[c]pyrrolo[3.2-e]indol-4(5H)-one

element) to the CBI element (cyclopropa[c]benz[e]indole-4-one element), carefully preserving the cyclopropa-indole-4-one moiety, which is the inherent alkylating activity (ref. 3).

Therefore as of the effective filing date of the above-identified application and currently, one of ordinary skill in the art, which includes the present inventors, readily recogniz(ed) analogs of CC-1065 as compounds that contain a cyclopropa-indole-4-one alkylating moiety, such as CPI or CBI, and a DNA binding element containing ring structures and that any of these compounds could be the CC-1065 analogs of the claimed prodrugs.

References with titles included.

1) M.A. Warpehoski, I. Gebhard, R.C. Kelly, W.C. Krueger, L.H. Li, J.P. McGovren, M.D. Prairie, N. Wicnienski, and W. Wierenga: Stereoelectronic factors influencing the biological activity and DNA interaction of synthetic antitumor agents modeled on CC-1065. *J. Med. Chem.* 31, 590-603 (1988).

2) D.L. Boger and S.A. Munk: DNA alkylation properties of enhanced functional analogs of CC-1065 incorporating the 1,2,9,9a-Tetrahydrocyclopropa[1,2-c]benz[1,2-e]indol-4-one (CBI) alkylation subunit. *J. Am. Chem. Soc.* 114(14), 5487-5496 (1992).

3) D.L. Boger, W. Yun, and B.R. Teegarden: An improved synthesis of 1,2,9,9a-Tetrahydrocyclopropa[c]benz[e]indol-4-one (CBI): a simplified analogue of the CC-1065 alkylation subunit. *J. Org. Chem.* 57, 2873-2876 (1992).

4) D.L. Boger and M.S.S. Palanki: Functional analogs of CC-1065 and the duocarmycins incorporating the 9a-(Chloromethyl)-1,2,9,9a-Tetrahydrocyclopropa[c]benz[e]indol-4-one (C_2BI) alkylation subunit: synthesis and preliminary DNA alkylation studies. *J. Am. Chem. Soc.* 114, 9318-9327 (1992).

5) D.L. Boger, D.S. Johnson, M.S.S. Palanki: Evaluation of functional analogs of CC-1065 and the duocarmycins incorporating the cross-linking 9a-(Chloromethyl)- 1,2,9,9a-Tetrahydrocyclopropa[c]benz[e]indol-4-one (C_2BI) alkylation subunit. *Bioorg. & Med. Chem.* 1(1), 27-38 (1993).

6) D.L. Boger and D.S. Johnson: CC-1065 and the duocarmycins: unraveling the keys to a new class of naturally derived DNA alkylating agents. *Proc. Natl. Acad. Sci.* USA 92, 3642-3649 (1995).

7) D.L. Boger, N. Han, C.M. Tarby, C. W. Boyce, H. Cai, Q. Jin, and P.A. Kitos: Synthesis, chemical properties, and preliminary evaluation of substituted CBI analogs of CC-1065 and the duocarmycins incorporating the 7-Cyano-1,2,9,9a-Tetrahydrocyclopropa[c]benz[e]indol-4-one alkylation subunit: Hammett quantitation of the magnitude of electronic effects on functional reactivity. *J. Org. Chem.* 61, 4894-4912 (1996).

8) Y. Wang, H. Yuan, W. Ye, S.C. Wright, H. Wang, and J.W. Larrick: Synthesis and preliminary biological evaluations of CC-1065 analogues: effects of different linkers and terminal amides on biological activity. *J. Med. Chem.* 43, 1541-1549 (2000).

9) D.L. Boger: Synthesis of CC-1065/Duocarmycin analogs. US Patent No. 6,310,209 B1, issued October 30, 2001.

10) M.J. Powell: Cyclopropylindole prodrugs. US Patent No. 5,646,298, issued July 8, 1997.

III. THE APPLICATION TEACHES ONE OF ORDINARY SKILL IN THE ART HOW TO MAKE AND USE A BROAD GROUP OF CC-1065 ANALOGS AND PRODRUGS THEREOF

CC-1065 is one of a few classes of extremely potent antitumor agents. It binds to double-stranded B-DNA within the minor groove with a sequence preference for 5'-d(A/GNTTA)-3' and 5'-d(AAAAA)-3', and alkylates the N3 position of the 3'-adenine with its left-hand CPI segment. CC-1065 also inhibits gene transcription by interfering with binding of the TATA box-binding protein to its target DNA. Despite its high potency and broad spectrum of antitumor activity, CC-1065 cannot be used in humans because it showed delayed, severe toxicity in experimental animals. Administration of CC-1065 to mice caused delayed hepatotoxicity leading to mortality on day 50 after a single intravenous dose of 12.5 μg/kg (1986, V. L. Reynolds et al., *J. Antibiotics*, **XXIX**, 319-334).

This spurred efforts to develop analogs that preserve the broad spectrum of antitumor activity but are devoid of the delayed toxicity. The synthesis and characterization of many such analogs modeled on CC-1065 was first described by M.A. Warpehoski et al. (1988, *J. Med. Chem.*, **31**:590-603. *Stereoeletronic factors influencing the biological activity and DNA interaction of synthetic antitumor agents modeled on CC-1065*) (ref. 1, cited above). In a second series of such analogs, the CPI or seco-CPI moiety of CC-1065 analogs was replaced by a cyclopropabenzindole (CBI) moiety or a seco-CBI moiety (1990, D.L. Boger et al., *J. Org. Chem.*, **55**:5823-5833, *Functinal analogs of CC-1065 and the duocarmycins incorporating the 1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (CBI) left-handed subunit*; 1991, D.L. Boger et al., *BioOrg. Med. Chem. Lett.*, **1**:115-120, *Synthesis and preliminary evaluation of (+)-CBI-indole$_2$: an enhanced functional analog of (+)-CC-1065;* U.S. patent No. 6,060,608). These

compounds maintain the high *in vitro* potency of the parental drug, without causing delayed toxicity in mice. Like CC-1065, these compounds are alkylating agents that bind to the minor groove of DNA in a covalent manner to cause cell death. However, clinical evaluation of the most promising analogs, Adozelesin and Carzelesin, has led to disappointing results (1996, B.F. Foster et al., *Investigational New Drugs*, 13:321-326 ; 1996, I. Wolff et al., *Clin. Cancer Res.*, 2:1717-1723). These drugs display poor therapeutic effects because of their high systemic toxicity.

To enhance the therapeutic efficacy of CC-1065 analog drugs, ImmunoGen, Inc., the assignee of the above-identified application, then prepared analogs of CC-1065 that could be chemically linked to a cell-binding agent. This enabled the preparation of novel cell-binding agent-drug conjugates for the targeted delivery of the cytotoxic agent to specific cell populations. (see e.g. U.S. patent No. 5,846,545). These analogs of CC-1065 contain a moiety at the terminal amide that allows chemical linkage to the cell-binding agent (see e.g. Figures 3 to 6 in U.S. patent No. 5,846,545). Such analogs with different substituents at the terminal amide were not only prepared by scientists at ImmunoGen, Inc., but also by other scientists, such as Wang Y. et al. (2000, *J Med Chem.*, 43:1541-1549, *Synthesis and preliminary biological evaluation of CC-1065 analogues: Effects of different linkers and terminal amides on biological activity*).

Therefore, the preparation of numerous compounds classified as CC-1065 analogs that can be used to make the prodrugs of the present claims is described in many scientific publications and is routine for one skilled in the art.

The instant application improves on the CC-1065 analogs described above by the formation of prodrugs of such CC-1065 analogs that can be linked to cell-binding agents.

Prodrug formation serves to increase the solubility in aqueous solutions and to stabilize the seco-CBI moiety of the CC-1065 analogs through the reaction of the phenolic hydroxyl group to introduce a protecting group.

The design and preparation of prodrugs is a well-known and described science. (see e.g. 2003, Bernard Testa & Joachim M. Mayer, *Hydrolysis in Drug and Prodrug Metabolism, Chemistry, Biochemistry, and Enzymology,* Wiley-VCH, Zurich, Chapter 1.2. *Principle of Prodrug Design*; Chapter 8. *Hydrolysis of Carboxylic Acid Ester Prodrugs*; Chapter 8.4. *Prodrugs of Active Alcohols and Phenols*; Chapter 9. *The Cleavage of Esters of Inorganic Acids*; Chapter 9.3. *Hydrolysis and Oxidative Cleavage of Organophosphates*; Chapter 9.3.2. *Hydrolysis of Medicinal Phosporic Acid Alkyl and Aryl Monoesters*). The prodrugs described in the instant application are prodrugs of an active phenol, therefore some chapters in the above reference book that specifically deal with such prodrugs are mentioned. Also there are many prodrugs of active phenols known, such as irinotecan·HCl, which is a water-soluble dipiperidinylcarbamate prodrug of the active phenol, camptothecin, etopophos is a water-soluble phosphoryl mono ester prodrug of the phenol drug, etoposide, aspirine is an ester prodrug of the phenol drug, salicylic acid, and estradiol acetate is an ester prodrug of the phenol drug, estradiol.

Therefore the preparation of phenol prodrugs with the appropriate characteristics is well studied and described in the scientific literature and is routine for one skilled in medicinal chemistry.

Accordingly, as of the effective filing date of the above-identified application, one of ordinary skill in the art could readily have made the claimed prodrugs from a variety of CC-1065 analogues.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Jan. 31, 2005

Walter A. Blättler, Ph.D.

Curriculum Vitae

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Education:

Swiss Federal Institute of Technology, Zurich (ETH Zürich)	M.S.	1973	Chemistry
Swiss Federal Institute of Technology, Zurich (ETH Zürich)	Dr.sc.nat.	1978	Chemistry

Research and Professional Experience:

1978 - 1981	Postdoctoral Fellow, Chemistry Department, Harvard University, Cambridge, MA
1981 - 1986	Associate in Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
1986 - 1987	Assistant Professor in Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
1987 - 1996	Lecturer in Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
1987 - 1994	Vice-President Research, ImmunoGen, Inc., Cambridge, MA
1994 - 1996	Senior Vice President, R & D, ImmunoGen, Inc., Cambridge, MA
1996 -	Executive Vice President, Science & Technology, ImmunoGen, Inc., Cambridge, MA

Publications:

1978

Blättler, W.A. (1978) Sterischer Verlauf der Bildung und Öffnung des Cyclopropanringes in der Biosynthese von Phytosterinen. Thesis, ETH, Zürich.

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